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Award Number: W81XWH-13-2-0009

TITLE: Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

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REPORT DATE: January 2015

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
January 2015	Annual	26 Dec 2013 – 25 Dec 2014

4. TITLE AND SUBTITLE
Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

5a. CONTRACT NUMBER
W81XWH-13-2-0009

5b. GRANT NUMBER
W81XWH-13-2-0009

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT (brief – 200 words approx.) of most significant finding during the research period.

The goals and tasks of Funding Year 2 encompassed continued recruiting, enrollment and data collection:

- Protocol successfully amended to broaden inclusion/exclusion criteria to include surgical amputations, AKAs, and phantom pain in multiple locations
- Approval received by National Amputee Coalition research committee to advertise in their website, e-newsletter, and national magazine; recruiting material developed, approved, and placed in publications
- Amputee support group outreach, prosthetics groups outreach, and clinic outreach conducted
- Data collection ongoing for all enrolled subjects
- Data Safety Monitoring Board monitoring ongoing
- 18 subjects enrolled for all centers (15 at Cleveland Clinic, 3 at UCSD, 0 at Palo Alto VA, 0 at Walter Reed)
- 10 subjects participated in the crossover treatment (8 at Cleveland, 2 at UCSD, 0 at Palo Alto VA, 0 at Walter Reed)
- 3 additional subjects currently scheduled at UCSD for the Quarter 1, Funding Year 3

15. SUBJECT TERMS nothing listed					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	16	19b. TELEPHONE NUMBER *(include area code)*

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Introduction:

This project is a randomized, double-masked, placebo-controlled, simultaneous parallel and crossover, human-subjects clinical trial to determine if ambulatory continuous peripheral nerve block (CPNB) is an effective treatment for intractable phantom limb pain following limb amputation. There is currently no reliable treatment for phantom limb pain, which resolves in only 16% of cases. This is a multicenter trial at five collaborating sites: Walter Reed National Military Medical Center, Naval Medical Center San Diego, Veterans Affairs Palo Alto, Cleveland Clinic, and the University of California, San Diego. To be included, subjects must have an existing upper or lower amputation and experience phantom limb pain at least 3 times each week for the previous 8 weeks. They will have perineural catheter(s) inserted and then randomized to receive one of two study solutions *via* their catheter(s) in a double-masked manner: either a local anesthetic (ropivacaine 0.5%) or placebo (normal saline). Catheters will be removed after 6 days of at-home infusion. Although not required, each subject has the option to return for the alternative treatment 4-16 weeks later (crossover infusion). The primary endpoint will be the difference in average phantom pain intensity at baseline and 4 weeks following the initial infusion as measured with the Numeric Rating Scale between treatment groups for the initial infusion. Secondary endpoints will involve intra- and inter-subject comparisons of additional measures of pain and health-related quality-of-life. This trial has a strong potential to identify the first reliably effective treatment for intractable phantom limb pain following limb amputation.

Body:

Statement of Work for Funding Years 1 and 2

Funding Year:	1			2
Months (Within Year):	1-4	5-8	9-12	
Register study on clinicaltrials.gov	x			
Initiate DSMB meetings	x			
DSMB meetings (every 6 months)		x	x	x
Report to medical monitor (every month)		x	x	x
Finalize protocol and study forms	x			
Hire/train research coordinators	x	x	x	
Site visits and training by UCSD coordinator	x			x
Submit study to individual IRBs and USAMRMC	x	x		
Site visits and training by Principal Investigator		x		x
Prepare data-entry platform at UCSD	x			
Send database letters (following IRB approval)		x	x	
Educate clinic contacts for referrals		x	x	
Order and prepare equipment	x	x		
Amputee support group outreach			x	x
Advertising study in publications/websites			x	x
Patient enrollment (following IRB approval)			x	x
Quality assurance			x	x
Interim analyses (at 25%, 50%, 75% enrollment)				x
Data collection & entry (Day 1 to Month 12)			x	x
Data cleaning and final statistical analysis				
Manuscript preparation: protocol description				x
Manuscript preparation: final results				
IRB closures at all enrolling centers				
Final report to USAMRMC				
Uploading results to ClinicalTrials.gov				
Results sent to all enrolled subjects				

The following is a report on each task listed in the above Statement of Work for Funding Year 2.

Tasks

1. DSMB Meetings every 6 months and reports to medical monitor
The Data Safety Board monitoring is ongoing. No interim analysis has been generated as we have not reached 25% enrollment, but this is anticipated during Funding Year 3.

2. Site visits and training by UCSD coordinator and Principal Investigator
Initial site visits and training were conducted by both the PI and the UCSD trial manager during Funding Year 1:
October 25, 2013: Cleveland Clinic
November 22, 2013: Palo Alto Veteran's Affairs
December 13, 2013: Walter Reed National Military Medical Center

The site visit for the Naval Medical Center San Diego was not conducted during Year 2 as anticipated, due to the fact that they did not complete their contract due to internal issues they could not surmount. Please see Section 3.

During Funding Year 2, the Principal Investigator conducted a site visit at the Cleveland Clinic on October 1-2, 2014. The other sites were not visited because they have not yet enrolled subjects.

3. Submit study to individual IRBs and USAMRMC (continued from Funding Year 1)
UCSD, the Cleveland Clinic, and Walter Reed National Military Medical Center all received IRB and USAMRMC approval to enroll during Funding Year 1.

Palo Alto Veterans Affairs was required to seek regulatory approval from its collaborating Stanford IRB, as well the VA IRB. Stanford IRB approval was received on August 13, 2013. The VA Palo Alto Health Care system approved the protocol during the 1st quarter of Funding Year 2 (January 15, 2014). The protocol was approved by the USAMRMC on January 30, 2014, during Funding Year 2, as anticipated.

In a letter from the IRB dated on April 3, 2014, the Naval Medical Center received approval to enroll backdated to November 13, 2013. However, they did not submit their application to the USAMRMC for approval as anticipated. NMCSD faced contractual issues they could not surmount, and the PI and Site Director agreed that they would not continue to seek approval to become an enrolling site.

4. Amputee support group outreach

- Amputee support groups have been contacted, including the local National Amputee Coalition support group meeting at Vibra Hospital in San Diego. A presentation on the study was done by the UCSD clinical trial manager, and approved recruiting material was distributed at the meetings.

5. Advertising study in publications/websites

- The National Amputee Coalition office was contacted and the study submitted to their Research Committee for approval to advertise in their print media, website, and e-newsletter. An amendment with new recruiting material specifically targeted to these publications was submitted and approved by the UCSD IRB on September 8, 2014.
- A full-page ad was placed in InMotion magazine, the national magazine of the Amputee Coalition. It was published in the November 2014 issue highlighting research and, due to the increased interest this ad generated, additional full-page ads were scheduled for December 2014, and January and February 2015.
- The National Amputee Coalition used IRB-approved text to advertise in their e-newsletter
- A google adwords pay-per-click advertisement was implemented linking to IRB-approved text

6. Patient enrollment (following IRB approval)

UCSD has enrolled three subjects, and has an additional 3 scheduled within the next three weeks. Fifteen subjects have been enrolled at Cleveland Clinic, including one subject who withdrew voluntarily on Day One.

Due to lower than anticipated enrollment progress, we proposed to broaden the inclusion/exclusion criteria. We found that the majority of need within combat-injured amputees is for those with bilateral amputation(s) and phantom pain in multiple locations, and those with above-the-knee amputation(s), which had originally been excluded. In addition, we found that there was significant need in the population with amputations for etiologies other than trauma (i.e., dysvascular etiologies), which had previously been excluded.

Therefore, we proposed to the Defense Department and to the IRB at each site a corrective action plan for lower than anticipated enrollment that included three revisions to allow us to complete our planned enrollment, but not compromise the original study objectives:

On 06/25/2014 we received approval from the UCSD IRB to amend the study protocol with the following three revisions:

1. To allow subjects with phantom pain in multiple locations to enroll
2. To allow subjects with above-the-knee amputations to enroll
3. To allow subjects with surgical amputations to enroll

Once these revisions were approved by all enrolling sites' IRBs and the USAMRMC HRPO, increased advertising was implemented. There was an immediate increase in

calls and expressed interest in the study; the UCSD study manager has been averaging at least 4 calls and emails per week since the increased advertising began. Many potential participants are from areas of the country far from the study centers and do not have the resources to travel. However, there have also been semi-local candidates who live close enough to drive to the centers who have responded, and, as stated above, there are three new subjects scheduled at UCSD within the next three weeks (Quarter 1, Funding Year 3).

7. Quality assurance
Quality assurance is ongoing with regard to subject data.

8. Data collection (Day 1 to Month 12)
Data collection was successfully begun with the participation of the first subject on December 16, 2013. Data collection is ongoing with new and crossover subjects according to the protocol.

9. Manuscript preparation: Due to lower than anticipated enrollment, this task has been moved to the end of funding year 3.

Key Research Accomplishments:
The goals and tasks of Funding Year 2 encompassed continued recruiting, enrollment and data collection:

- Protocol successfully amended to broaden inclusion/exclusion criteria to include surgical amputations, AKAs, and phantom pain in multiple locations
- Approval received by National Amputee Coalition research committee to advertise in their website, e-newsletter, and national magazine; recruiting material developed, approved, and placed in publications
- Amputee support group outreach, prosthetics groups outreach, and clinic outreach conducted
- Data collection ongoing for all enrolled subjects
- Data Safety Monitoring Board monitoring ongoing
- 18 subjects enrolled to date for all centers (15 at Cleveland Clinic, 3 at UCSD)
- 10 subjects (8 at Cleveland, 2 at UCSD) participated in the crossover treatment
- 3 additional subjects scheduled at UCSD for Quarter 1 of Funding Year 3

Reportable Outcomes:
Not applicable. The goals and tasks of Funding Year 2 encompassed continued recruitment, enrolling, and data collection.

Conclusion:
This is a randomized, triple-masked, placebo-controlled clinical trial that will remain masked until enrollment is completed and the final value for the primary endpoint has been collected.

References:
Not applicable

Appendices:
Study questionnaires are on the following pages 7 to 10.
Actual and projected enrollment tables are on pages 11 to 12.

Beck Depression Inventory: Day 0
(Initial or Crossover Treatment)

Randomization Number: ____ - ____ - ____ ____ ____ *[fill in following randomization]*

Subject Initials: ____ ____ ____

Administered by (initials): ___ ___

Questionnaire Date: ____ / ____ / 201 ____

Time point: □ Initial □ Crossover

Circle the correct number for each question:

1) Sadness:
0 You do not feel sad.
1 You feel sad much of the time
2 You are sad all the time.
3 You are so sad or unhappy that you can't stand it

2) Pessimism:
0 You are not discouraged about your future.
1 You feel more discouraged about your future than you used to be.
2 You do not expect things to work out for yourself.
3 You feel your future is hopeless and will only get worse.

3) Past Failure:
0 You do not feel like a failure.
1 You have failed more than you should have
2 As you look back, you see a lot of failures.
3 You feel you are a total failure as a person.

4) Loss of Pleasure:
0 You get as much pleasure as you ever did from things you enjoy.
1 You don't enjoy things as much as you used to.
2 You get very little pleasure from the things you used to enjoy.
3 You can't get any pleasure from the things you used to enjoy.

[Continued on following page]

5) Guilty Feelings:
0 You don't feel particularly guilty.
1 You feel guilty over many things you have done or should have done.
2 You feel quite guilty most of the time.
3 You feel guilty all the time.

6) Punishment Feelings:
0 You don't feel you are being punished.
1 You feel you may be punished.
2 You expect to be punished.
3 You feel you are being punished.

7) Self-Dislike:
0 You do not feel sad.
1 You feel sad much of the time.
2 You are sad all the time.
3 You are so sad or unhappy that you can't stand it.

8) Self-Criticalness:
0 You don't criticize or blame yourself more than usual.
1 You are more critical of yourself than you used to be.
2 You criticize yourself for all of your faults.
3 You blame yourself for everything bad that happens

9) Suicidal Thoughts or Wishes:
0 You don't have any thoughts of killing yourself.
1 You have thoughts of killing yourself, but you would not carry them out. *
2 You would like to kill yourself. *
3 You would kill yourself if you had the chance. *
*contact Site Director at end of questionnaire

10) Self-Dislike:

0 You don't cry any more than you used to.
1 You cry more than you used to.
2 You cry over every little thing.
3 You feel like crying, but you can't.

11) Agitation:

0 You are no more restless or wound up than usual.
1 You feel more restless or wound up than usual.
2 You are so restless or agitated that it's hard to stay still.
3 You are so restless or agitated that you have to keep moving or doing something.

12) Loss of Interest:

0 You have not lost interest in other people or activities.
1 You are less interested in other people or things than before.
2 You have lost most of your interest in other people or things.
3 It's hard to get interested in anything.

13) Indecisiveness:

0 You make decisions about as well as ever.
1 You find it more difficult to make decisions than usual.
2 You have much greater difficulty in making decisions than you used to.
3 You have trouble making any decisions.

14) Worthlessness:

0 You do not feel you are worthless.
1 You don't consider yourself as worthwhile and useful as you used to.
2 You feel more worthless as compared to other people.
3 You feel utterly worthless.

15) Loss of Energy:

0 You have as much energy as ever.
1 You have less energy than you used to have.
2 You don't have enough energy to do very much. 3 You don't have enough energy to do anything.

16) Changes in Sleeping Pattern:

0 You have not experienced any change in your sleeping pattern.
1a You sleep somewhat more than usual.
1b You sleep somewhat less than usual.
2a You sleep a lot more than usual.
2b You sleep a lot less than usual.
3a You sleep most of the day.
3b You wake up 1-2 hours early and can't get back to sleep.

17) Irritability:

0 You are no more irritable than usual.
1 You are more irritable than usual.
2 You are much more irritable than usual.
3 You are irritable all the time.

18) Changes in Appetite:

0 You have not experienced any change in appetite.
1a Your appetite is somewhat less than usual.
1b Your appetite is somewhat greater than usual.
2a Your appetite is much less than before.
2b Your appetite is much greater than usual.
3a You have no appetite at all.
3b You crave food all the time.

19) Concentration Difficulty:

0 You can concentrate as well as ever.
1 You can't concentrate as well as usual.
2 It's hard to keep your mind on anything for very long.
3 You find you can't concentrate on anything.

20) Tiredness of Fatigue:

0 You are no more tired or fatigued than usual.
1 You get more tired or fatigued more easily than usual.
2 You are too tired or fatigued to do a lot of the things you used to do.
3 You are too tired or fatigued to do most of the things you used to do.

21) Loss of Interest in Sex:

0 You have not noticed any recent change in your interest in sex.
1 You are less interested in sex than you used to be.
2 You are much less interested in sex now.
3 You have lost interest in sex completely

Data Collection Form: Day 28
(Initial or Crossover Treatment)

Randomization Number: ____ - ____ - ____ ____ ____

Subject Initials: ____ ____ ____

Treatment: ☐ Initial ☐ Crossover

Administered by (initials): ___ ___

Questionnaire Date: ____ / ____ / 201 ____

Read aloud: *I am going to ask you some questions referring to pain in your limb being treated. Stump pain is defined as painful sensations located in the portion of the limb still physically present. Phantom limb pain is defined as painful sensations experienced where there is no longer a limb. First, I will ask you about any* ***phantom limb pain*** *you may be having.*

On a scale from 0-10, with 0 equal to 'no pain' and 10 equal to 'worst imaginable pain':

1a) How would you describe your phantom limb pain at its WORST in the last three days? ____ ____

2a) How would you describe your phantom limb pain at its LEAST in the last three days? ____ ____

3a) How would you describe your phantom limb pain on AVERAGE in the last three days? ____ ____

4a) How would you describe how much phantom limb pain you have RIGHT NOW? ____ ____

The next questions use the same 0-10 scale, but now refer to your RESIDUAL LIMB or STUMP pain:

1b) How would you describe your stump pain at its WORST in the last three days? ____ ____

2b) How would you describe your stump pain at its LEAST in the last three days? ____ ____

3b) How would you describe your stump pain on AVERAGE in the last three days? ____ ____

4b) How would you describe how much stump pain you have RIGHT NOW? ____ ____

On a scale from 0%-100%, with 0% equal to 'no relief' and 100% equal to 'complete relief':

How much relief have pain treatments or medications provided in the last three days for your:

5a) PHANTOM LIMB pain? ____ ____ ____ %

5b) STUMP pain? ____ ____ ____ %

The next questions refer only to your phantom limb pain. On a scale from 0-10, with 0 equal to 'does not interfere' and 10 equal to 'completely interferes':

In the last three days, how has your *phantom limb pain* interfered with [must answer all]:

6a) General Activity ____ ____

7a) Mood ____ ____

8a) Walking ability ____ ____

9a) Normal work (includes both work outside the home and housework) ____ ____

10a) Relations with other people ____ ____

11a) Sleep ____ ____

12a) Enjoyment of life ____ ____

Patient Global Impression of Change Scale (PGIC)

How much improvement you have had in your phantom limb pain ***since the very first catheter was placed****:*

Very much worse			No change			Very much improved
1	2	3	4	5	6	7

Now, I am going to ask about the frequency and duration of phantom limb pain [record "99" for continuous]**.**

13a) How many times in the last three days have you experienced **phantom limb** pain? ____ ____

14a) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

13c) How many times in the last three days have you experienced **non-painful phantom sensations** in the lost body part? ____ ____

14c) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

6b) How many times in the last three days have you experienced **stump** pain? ____ ____

7b) How many minutes/hours did each episode last, on average (circle m/h): ____ ____ min / hour

Which study fluid do you believe you received during your most-recent infusion:

☐ Definitely active ☐ Probably active ☐ Don't know ☐ Probably saline ☐ Definitely saline

Actual Quarterly Enrollment

	Year 1				Year 2				Total
Actual Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
Site #1 UCSD				1				2	3
Site #2 Cleveland Clinic					3	1	8	3	15
Site #3 VA Palo Alto									0
Site #4 WRNMMC									0
Site #5 NMCSD									0
Actual Enrollment (cumulative)	**0**	**0**	**0**	**1**	3	1	8	5	**18**

	Year 3				Year 4				Total
Actual Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
Site #1 UCSD	(3)								
Site #2 Cleveland Clinic									
Site #3 VA Palo Alto									
Site #4 WRNMMC									
Site #5 NMCSD									
Actual Enrollment (cumulative)									

Projected Quarterly Enrollment

	Year 1				Year 2				Total
Target Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
Site #1 UCSD					4	4	4	4	16
Site #2 Cleveland Clinic					4	4	4	4	16
Site #3 VA Palo Alto					4	4	4	4	16
Site #4 WRNMMC					3	3	3	3	12
Site #5 NMCSD					3	3	3	3	12
Target Enrollment (cumulative)	**0**	**0**	**0**	**0**	**18**	**18**	**18**	**18**	**72**

	Year 3				Year 4				Total
Target Enrollment (per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	
Site #1 UCSD	5	4	5	4					18
Site #2 Cleveland Clinic	5	4	5	4					18
Site #3 VA Palo Alto	4	5	4	5					18
Site #4 WRNMMC	4	5	4	5					18
Site #5 NMCSD	0	0	0	0					18
Target Enrollment (cumulative)	**18**	**18**	**18**	**18**	**0**	**0**	**0**	**0**	**144**